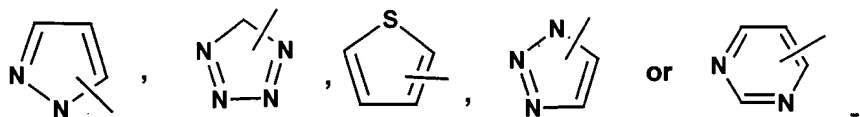


$\text{---C}(\text{NR}^8\text{R}^9)=\text{CH---C}(=\text{O})\text{---R}^{8a}$ ; tetrazolyl, pyrazolyl, pyridyl, thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole,  $\text{---PO}(\text{R}^{13})(\text{R}^{14})$ , (where  $\text{R}^{13}$  and  $\text{R}^{14}$  are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); and may be optionally independently substituted with from one to five substituents, which may be the same or different; including pharmaceutically acceptable salts thereof, prodrugs thereof, and all stereoisomers thereof. --

--71. (Amended) The compound as defined in Claim 64 wherein  $\text{R}^1$  is



#### REMARKS

Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 20, 22, 24 to 31 and new Claims 63 to 74 are present for purposes of prosecution.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.


Claim 1 is rejected under 35 USC 112, first paragraph in view of the provisos included in the previously amended Claim 1.

All provisos have been removed from Claims 1 and 64.

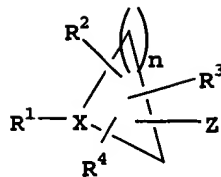
Claim 14 and claims dependent thereon are rejected on use of the zig zag symbol. The zig zag symbols have been replaced with the Z group as shown in Claim 1.

In view of the above, it is believed that all formal objections have been overcome.

Claim 1 and Claim 64 have been amended to include heteroaryl rings (for  $\text{R}^1$ ) as set out on

page 18 of the specification and the group  set out in Claim 19.

Applicants' invention as claimed in Claim 1 is directed to a compound having the structure

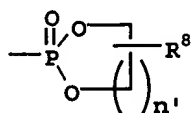


wherein n is 4;

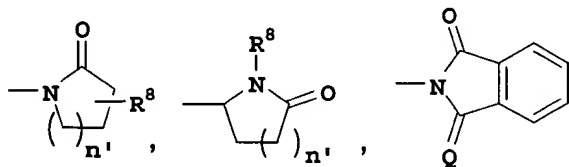
X is N;

Z is a heteroaryl group;

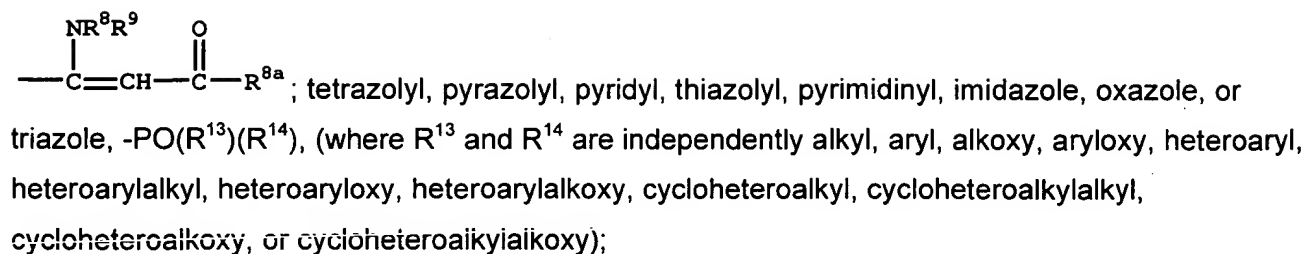
R<sup>1</sup> is alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)<sub>3</sub>Si (where each alkyl or aryl group is independent), cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl, polyhaloalkoxy, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heteroarylaminocarbonyl, hydroxy, acyl, carboxy, alkylcarbonylamino, arylcarbonyloxy, arylcarbonylamino, heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, alkoxycarbonylamino, I,I-(alkoxyl or aryloxy)<sub>2</sub>alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring), S(O)<sub>2</sub>R<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkenyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkynyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)heteroaryl, -NR<sup>8</sup>(C=NCN)-amino,



pyridine-N-oxide,



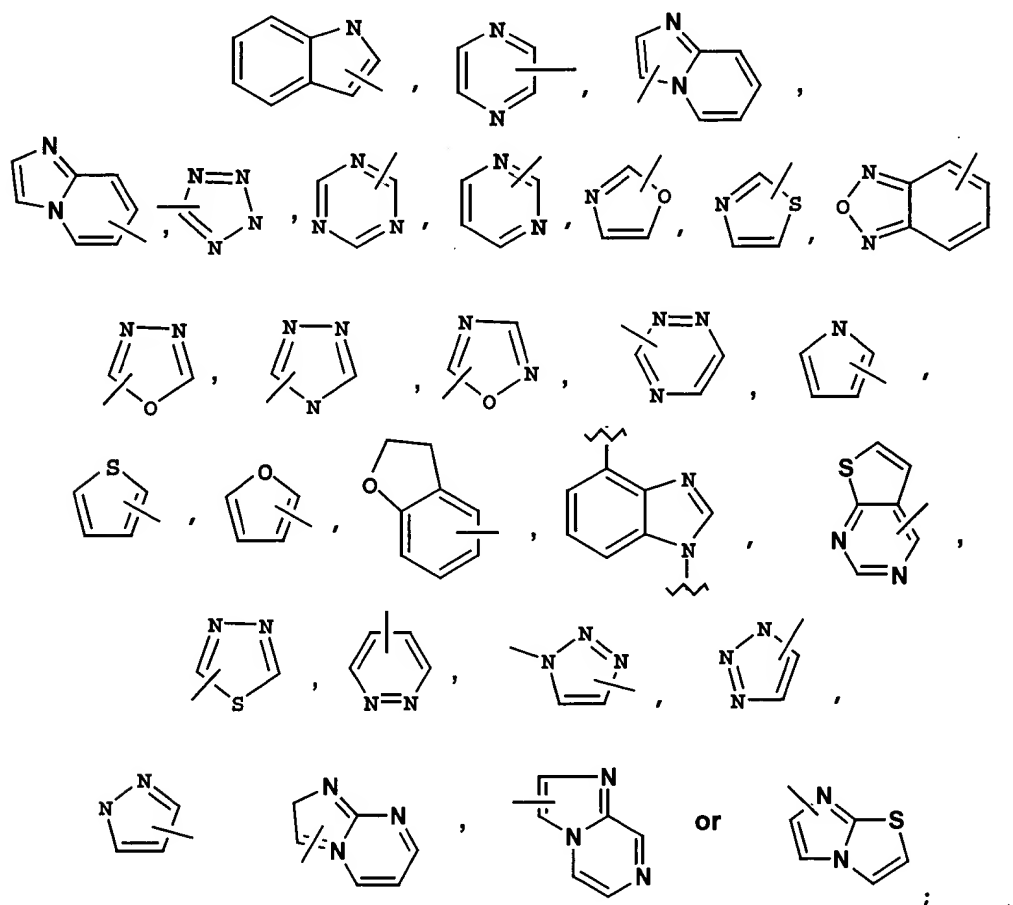
(where Q is O or H<sub>2</sub> and n' is 0, 1, 2 or 3) or



R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>8a</sup> and R<sup>9</sup> are the same or different and are independently hydrogen, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, or cycloheteroalkyl;

and R<sup>1</sup> may be unsubstituted or substituted with from one to five substituents;

and wherein the R<sup>1</sup> heteroaryl group is selected from



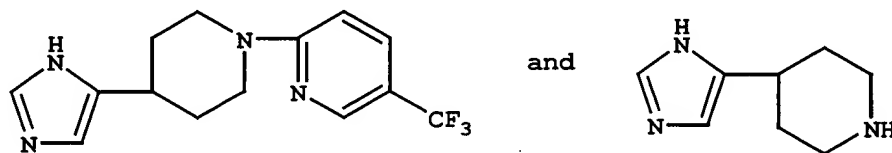
R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and are independently any of the groups originally set out for R<sup>1</sup> and may be optionally independently substituted with from one to five substituents, which may be the same or different;

including pharmaceutically acceptable salts thereof, prodrugs thereof, and all stereoisomers thereof.

It is submitted that Applicants' invention as now claimed is patentable over all cited references each taken alone or in any combination.

Claims 1-4, 6-10, 12, 13, 15-19, 22, 24, 25, 31, and Claims 64-70 are rejected under 35 U.S.C. 102(b) as being anticipated by Ganellin et al, Chem Abstract 123:198692, in that "pyridine anticipates heteroaryl".

Ganellin et al disclose compounds of the structure



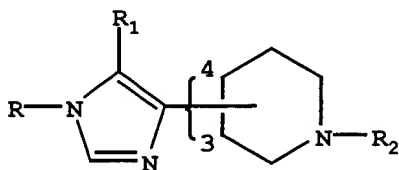
As indicated by the Examiner, Ganelli et al disclose compounds where "the corresponding R<sup>1</sup> is pyridine and Z is imidazole."

Claim 1 has been amended so that pyridyl and H are no longer encompassed by R<sup>1</sup>.

In view of the foregoing, it is submitted that Claims 1, 3, 6, 8 to 10, 14, 15, 17, 19, 22, 24, 25 and 31 and Claim 64 are patentable over Ganellin et al.

Claims 1, 2, 4, 6-10, 12, 14-16, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Arrang et al (US Patent 4,707,487) and also under 35 USC 103(a). The Examiner contends that Arrang reads on R<sup>1</sup> as aminocarbonyl.

U.S. Patent No. 4,707,487 to Arrang et al discloses (4-imidazolyl)-piperidines of the formula

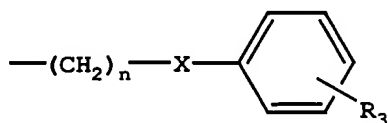


in which

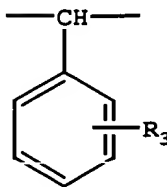
R<sub>1</sub> denotes a hydrogen atom or a methyl or ethyl group,

R denotes a hydrogen atom or a radical R<sub>2</sub>, and

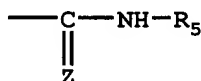
R<sub>2</sub> denotes a linear or branched alkyl group having 1 to 6 carbon atoms; a piperonyl group; a 3-(1-benzimidazolonyl)propyl group; a group of formula



in which n is 0, 1, 2 or 3, X is a single bond or alternatively -O-, -S-, -NH-, -CO-, -CH=CH- or



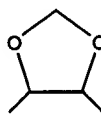
and  $R_3$  is H,  $CH_3$ , halogen, CN,  $CF_3$  or an acyl group  $-COR_4$ ,  $R_4$  being a linear or branched alkyl group having 1 to 6 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms or a phenyl group which can bear a  $CH_3$  or F substituent; or alternatively a group of formula



in which Z denotes an O or S atom or a divalent group NH, N- $CH_3$  or N-CN and  $R_5$  denotes a linear or branched alkyl group having 1 to 8 carbon atoms, a cycloalkyl group having 3 to 6 carbon atoms which can bear a phenyl substituent, a cycloalkyl (3 to 6 C) alkyl (1 to 3 C, linear or branched) group, a phenyl group which can bear a  $CH_3$ , halogen or  $CF_3$  substituent, a phenylalkyl (1 to 3 C, linear or branched) group or a naphthyl, adamantyl or p-toluenesulphonyl group, as well as the pharmaceutically acceptable salts thereof.

$R_2$  in the Arrang et al compounds (correspond to Applicants'  $R^1$  group) includes

(1) alkyl



(2) piperonyl (a phenylmethyl group having a fused to the phenyl group -- thus piperonyl is an arylalkyl group)

(3) 3-(1-benzimidazolonyl)propyl (that is, a cycloheteroalkyl group)

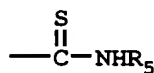
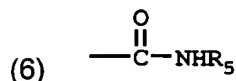
(4) (a) phenyl

(b) phenylalkyl

(c) phenyl-X- (where X is a bond, O, S, NH, CO, -CH=CH- or phenylmethylene)

(d) phenyl-X-alkyl

(5) acyl ( $COR_4$ - where  $R_4$  is alkyl, cycloalkyl or phenyl)



where  $R_5$  is alkyl, cycloalkyl, cycloalkylalkyl, phenyl, naphthyl, adamantyl or p-toluenesulfonyl.

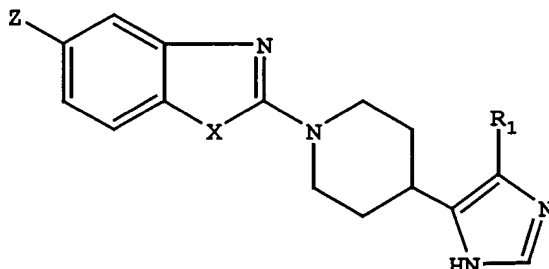
Claim 1 has been amended to delete from the definition of  $R^1$  the term aminocarbonyl.

Thus, the amended definition of R<sup>1</sup> no longer encompasses any of the R<sub>2</sub> groups of Arrang et al.

In view of the foregoing, it is submitted that Applicants' compounds as claimed in Claims 1, 2, 6, 8 to 10, 14-16, 22, 24, 25, 31 and Claim 64 are patentable over Arrang et al.

Claims 1-4, 6-10, 12, 13, 15-18, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Jagham et al (US Patent 5,280,030) and also under 35 USC 103(a). The Examiner contends that this reference discloses a bicyclic ring which anticipates heteroaryl.

Jagham et al disclose a piperidine derivative of formula (I)



in which R<sub>1</sub> represents a hydrogen atom, a linear or branched (C<sub>1-6</sub>)alkyl group or a cyclo(C<sub>3-8</sub>)alkyl group, X represents an oxygen atom, a sulphur atom or a group of general formula N-R<sub>3</sub> in which R<sub>3</sub> is a hydrogen atom, or a linear or branched (C<sub>1-8</sub>)alkyl, cyclo(C<sub>3-6</sub>)alkyl, cyclo(C<sub>3-6</sub>)alkylmethyl, (C<sub>1-4</sub>)alkoxy-(C<sub>1-4</sub>)alkyl, phenyl, pyridin-4-yl, pyridin-3-yl, pyridin-4-ylmethyl or pyridin-3-ylmethyl group and Z represents a hydrogen or fluorine atom and acid addition salts thereof with pharmaceutically acceptable acids.

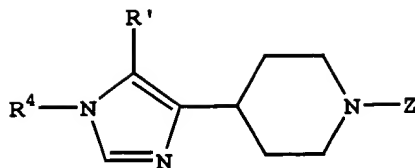
Thus, the Jagham et al bicyclic group linked to the N of the piperidine includes a benzimidazole, a benzthiazole or a benzoxazole.

Please note that Claim 1 has been amended so that the R<sup>1</sup> group no longer includes a benzimidazole, a benzthiazole or a benzoxazole.

In view of the foregoing, it is submitted that Claims 1 to 3, 6, 8 to 10, 12-13, 15-18, 22, 24, 25, 31 and Claims 64-70 are patentable over Jagham et al (5,280,030).

Claims 1, 2, 4, 6, 8-10, 12, 14, 16, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Durant et al (US Patent 5,663,350) and also under 35 USC 103(a). The Examiner contends that Durant teaches that R<sup>2</sup> can be piperonyl.

Durant et al disclose compounds of the structure



wherein Z is



or R<sup>2</sup>;

R' is H or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>1</sup> is OR<sup>2</sup>, (CH<sub>2</sub>)<sub>n</sub>R<sup>3</sup>, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>1</sub>-C<sub>20</sub> alkenyl, C<sub>1</sub>-C<sub>20</sub> cycloalkyl, C<sub>1</sub>-C<sub>20</sub> cycloalkenyl and C<sub>1</sub>-C<sub>20</sub> alkylaryl;

R<sup>2</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl, piperonyl or (CH<sub>2</sub>)<sub>n</sub>R<sup>3</sup>;

R<sup>3</sup> is adamantyl methyl, C<sub>1</sub>-C<sub>20</sub> cycloalkyl, C<sub>1</sub>-C<sub>20</sub> cycloalkyl phenyl methylene, C<sub>1</sub>-C<sub>20</sub> dicycloalkyl methylene, diphenyl methylene, Y-C<sub>6</sub>H<sub>4</sub>-R<sup>5</sup>



R<sup>4</sup> is H,



or C<sub>1</sub>-C<sub>4</sub> alkyl;

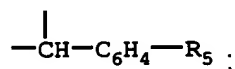
R<sup>5</sup> is H, CH<sub>3</sub>, halogen, CN, CF<sub>3</sub> or COR<sup>6</sup>;

R<sup>6</sup> is C<sub>1</sub>-C<sub>20</sub> linear or branched chain alkyl, C<sub>1</sub>-C<sub>20</sub> cycloalkyl, phenyl or phenyl substituted with 1-3 substituents selected from the group consisting of CH<sub>3</sub> or F;

R<sup>7</sup> is C<sub>1</sub>-C<sub>20</sub> linear or branched chain alkyl, C<sub>1</sub>-C<sub>20</sub> cycloalkyl phenyl methylene, C<sub>1</sub>-C<sub>20</sub> cycloalkyl alkyl methylene, C<sub>1</sub>-C<sub>20</sub> dicycloalkyl methylene, phenyl, phenyl substituted with 1-3 substituents selected from the group consisting of CH<sub>3</sub>, halogen, C<sub>1</sub>-C<sub>3</sub> alkyl (linear or branched);

X is S or O;

Y is a single bond or alternatively -O-, -S-, -NH-, -CO-, -CH=CH- or



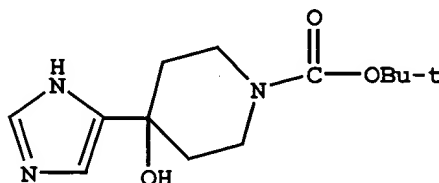
W is O, S, NH, NCH<sub>3</sub> or NCN; and n=0-10.

Applicants' Claim 1 has been amended so that R<sup>1</sup> no longer includes piperonyl.

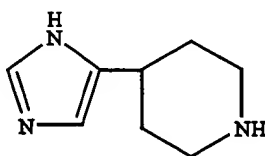
In view of the above amendments to the definition of R<sup>1</sup>, it is submitted that Applicants' compounds as claimed in Claims 1 to 3, 6, 8 to 10, 14, 22, 24, 25, 31 and Claims 64-70 are patentable over Durant et al.

Claims 1, 2, 4, 6, 10, 12, 14-16, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Lange et al, Chem Abstract 124:965601. The Examiner contends that Lange et al teach a carboxy group attached to the N of the piperidine ring.

Lange et al disclose compounds of the structure



and

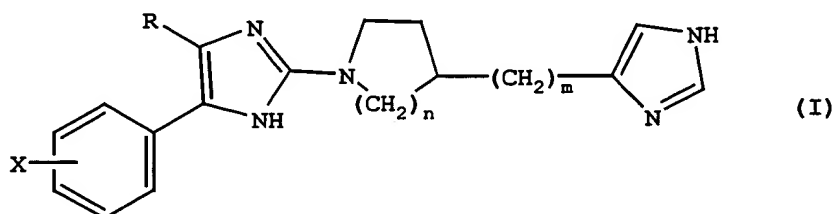


Claim 1 has been amended to delete alkylcarbonyloxy from the definition of R<sup>1</sup>.

In view of the above amendments to the definition of R<sup>1</sup>, it is submitted that Applicants' compounds as claimed in Claims 1, 2, 6, 8 to 10, 14, 15, 22, 24, 25 and 31 and Claim 64 are patentable over Lange et al.

Claims 1-3, 6, 8-10, 14, 15, 17, 19, 20, 22, 24-27, 31, and 64-74 are rejected under 35 USC 102(b) as being anticipated by Jegham et al and also under 35 USC 13(a).

Jegham et al disclose compounds of the structure



where R represents a hydrogen atom or a phenyl group optionally substituted by a halogen atom or a methyl, methoxy, trifluoromethyl or nitro group; X represents a hydrogen or halogen atom or a methyl, methoxy, trifluoromethyl or nitro group; n is equal to 1 or 2, and m is equal to 0 or 1.

Applicants have amended Claim 1 and Claim 64 so that R<sup>1</sup> includes specific heteroaryl groups none of which includes the 2-imidazolyl present in Jegham et al.



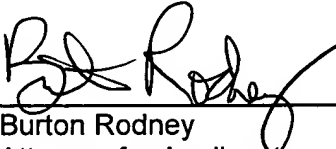
Accordingly, it is submitted Jegham et al does not disclose or suggest Applicants' compounds as now claimed. Thus, it is believed that Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 20, 22, 24 to 27, 31, and 64 to 74 are patentable over Jegham et al.

In view of the foregoing, it is submitted that Claims 1 to 3, 6, 8 to 10, 14, 15, 17, 19, 20, 22, 24 to 31 and Claims 63 to 74 overcome all formal objections and are patentable over all cited prior art. Accordingly, it is believed that the above claims are in condition of allowance.

Applicants note with appreciation that Claims 28 to 30 and 63 are allowable.

Respectfully submitted,

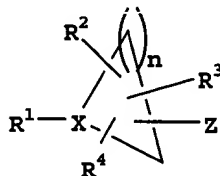
Bristol-Myers Squibb Company  
Patent Department  
P.O. Box 4000  
Princeton, NJ 08543-4000  
(609) 252-4336

  
\_\_\_\_\_  
Burton Rodney  
Attorney for Applicants  
Reg. No. 22,076

Date: *March 27, 2002*

MARKED-UP VERSION OF AMENDED CLAIMS

--1. (Twice Amended) A compound having the structure

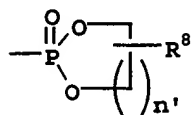


wherein n is 4;

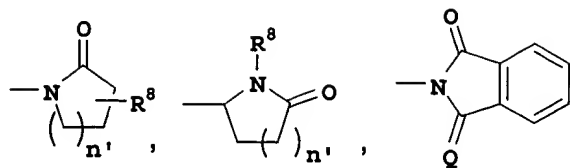
X is N;

Z is a heteroaryl group;

R<sup>1</sup> is alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)<sub>3</sub>Si (where each alkyl or aryl group is independent), cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroaryl amino, heteroaryloxy, arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl, polyhaloalkoxy, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, heteroarylaminocarbonyl, hydroxy, acyl, carboxy, [aminocarbonyl,] [alkylcarbonyloxy,] alkylcarbonylamino, arylcarbonyloxy, arylcarbonylamino, heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, alkoxycarbonylamino, I,I-(alkoxy or aryloxy)<sub>2</sub>alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring), S(O)<sub>2</sub>R<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkenyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkynyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)heteroaryl, -NR<sup>8</sup>(C=NCN)-amino,



pyridine-N-oxide,



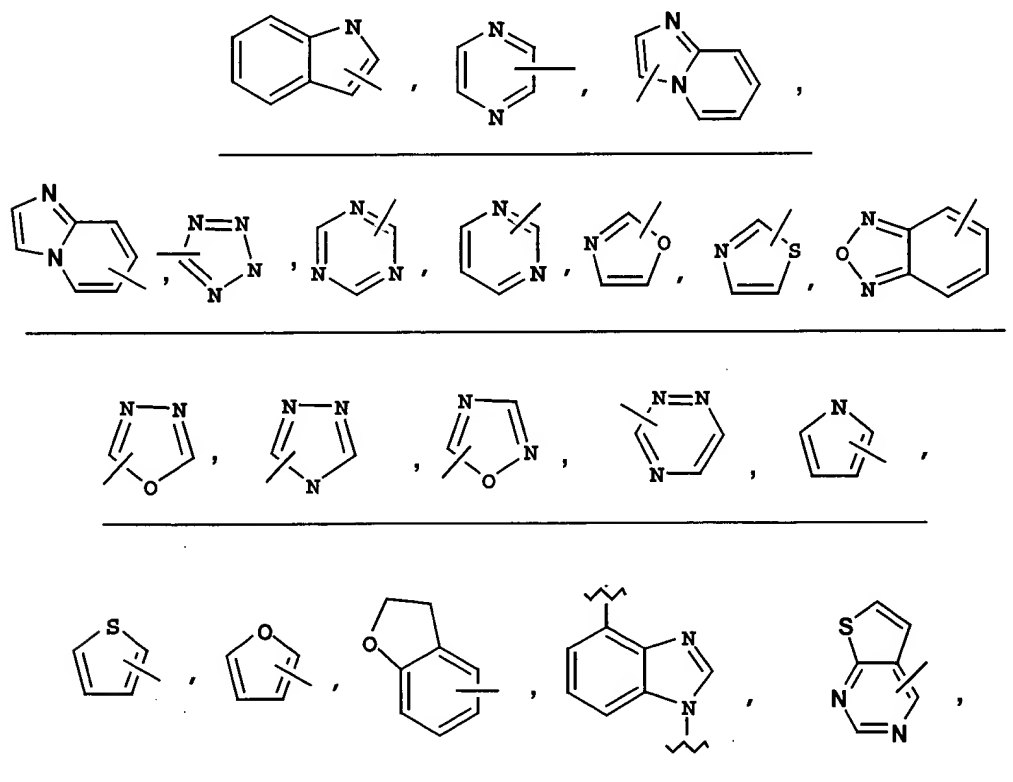
(where Q is O or H<sub>2</sub> and n' is 0, 1, 2 or 3) or

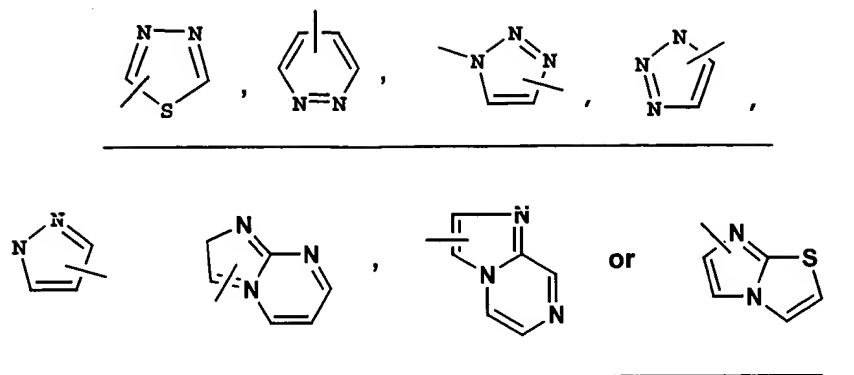
$\text{—C}(\text{NR}^8\text{R}^9)=\text{CH—C}(=\text{O})\text{—R}^{8a}$ ; tetrazolyl, pyrazolyl, thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole, -PO(R<sup>13</sup>)(R<sup>14</sup>), (where R<sup>13</sup> and R<sup>14</sup> are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy);

R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>8a</sup> and R<sup>9</sup> are the same or different and are independently hydrogen, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, or cycloheteroalkyl;

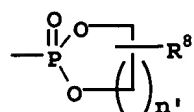
and R<sup>1</sup> may be unsubstituted or substituted with from one to five substituents;

and wherein the R<sup>1</sup> heteroaryl group is selected from

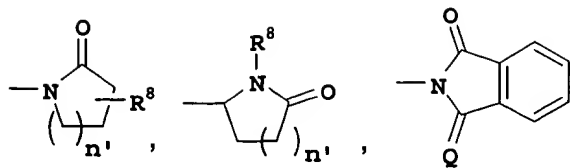




$R^2$ ,  $R^3$  and  $R^4$  are the same or different and are independently H, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)<sub>3</sub>Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroarylamino, heteroaryloxy, arylthio, arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl, polyhaloalkoxy, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, hydroxy, acyl, carboxy, aminocarbonyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonyl, arylcarbonyloxy, arylcarbonylamino, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, alkoxycarbonylamino, 1,1-(alkoxyl or aryloxy)<sub>2</sub>alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring),  $S(O)_2R^6R^7$ ,  $-NR^6(C=NR^7)alkyl$ ,  $-NR^6(C=NR^7)alkenyl$ ,  $-NR^6(C=NR^7)alkynyl$ ,  $-NR^6(C=NR^7)heteroaryl$ ,  $-NR^8(C=NCN)-amino$ ,



pyridine-N-oxide,

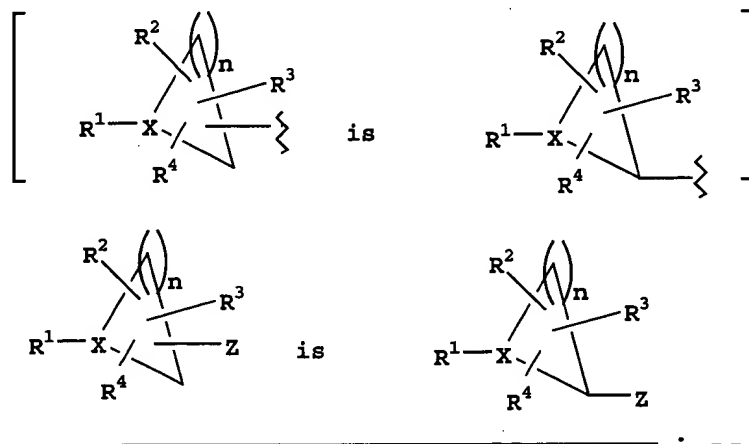


(where Q is O or H<sub>2</sub> and n' is 0, 1, 2 or 3) or

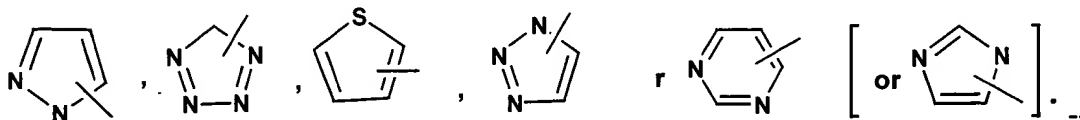
$\text{---C}(\text{NR}^8\text{R}^9)=\text{CH---C}(=\text{O})\text{---R}^{8a}$ ; tetrazolyl, pyrazolyl, pyridyl, thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole,  $\text{---PO}(\text{R}^{13})(\text{R}^{14})$ , (where R<sup>13</sup> and R<sup>14</sup> are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); and may be optionally independently substituted with from one to five substituents, which may be the same or different;

including pharmaceutically acceptable salts thereof, prodrugs thereof, and all stereoisomers thereof; with the provisos that (1) where Z is imidazol-4-yl or 5-alkylimidazol-4-yl or 5-cycloalkylimidazol-4-yl, then R<sup>1</sup> cannot be or include a benzoxazole, benzthiazole, or benzimidazole and (2) R<sup>1</sup> is exclusive of 3-(1-benzimidazolonyl)-propyl]. --

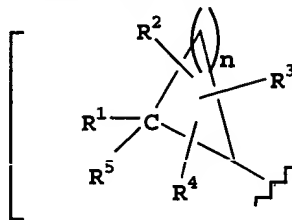
--14. (Amended) The compound as defined in Claim I wherein the moiety



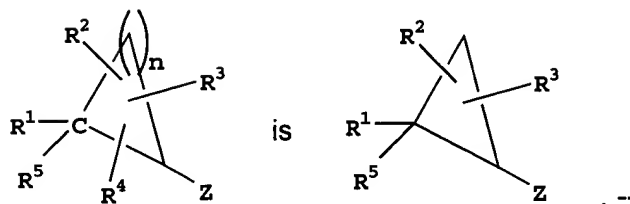
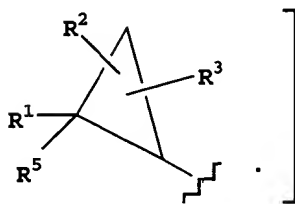
--19. (Twice Amended) The compound as defined in Claim I wherein R<sup>1</sup> is



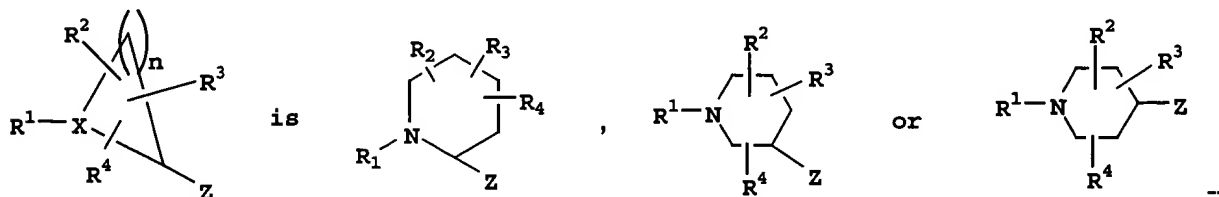
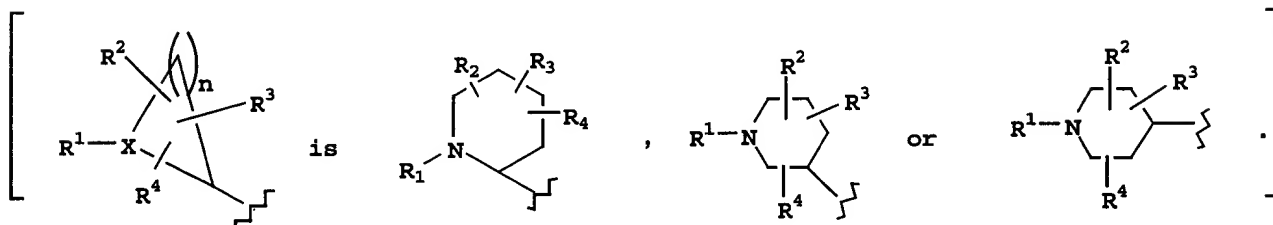
--21. (Amended) The compounds as defined in Claim 11 wherein



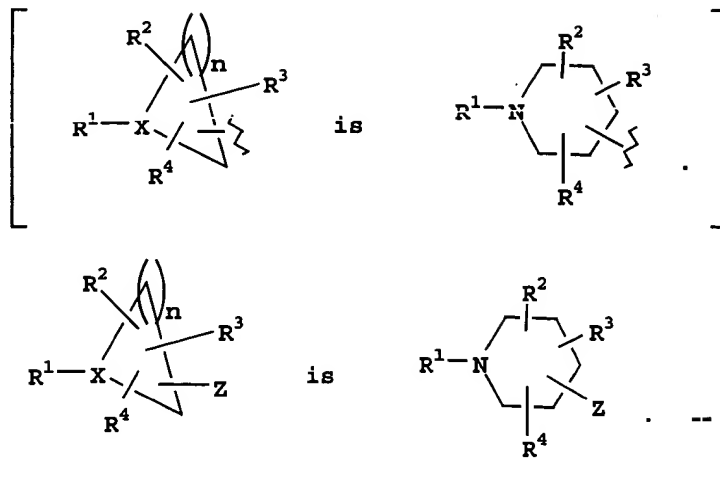
is



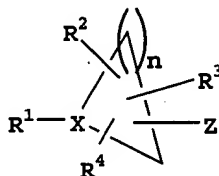
--22. (Twice Amended) The compound as defined in Claim 14 wherein



--24. (Twice Amended) The compound as defined in Claim 14 wherein



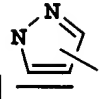
--64. (Amended) A compound having the structure



wherein n is 4;

X is N;

Z is a heteroaryl group;

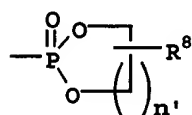
R<sup>1</sup> is [heteroaryl] tetrazolyl, pyrazolyl, thiazolyl, pyrimidinyl, [imidazole,] , oxazole, or triazole;

R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>8a</sup> and R<sup>9</sup> are the same or different and are independently hydrogen, alkyl, haloalkyl, aryl, heteroaryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, or cycloheteroalkyl;

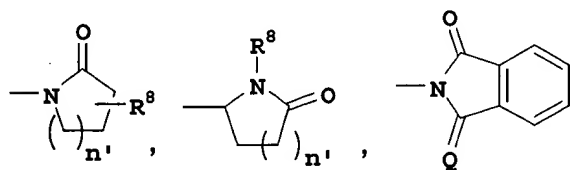
and R<sup>1</sup> may be unsubstituted or substituted with from one to five substituents;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are the same or different and are independently H, alkyl, alkenyl, alkynyl, alkoxy, alkenyloxy, alkynyloxy, (alkyl or aryl)<sub>3</sub>Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, heteroarylalkyl, heteroaryloxy, arylthio, arylsulfinyl, arylsulfonyl, thio, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, halogen, haloalkyl, polyhaloalkyl,

polyhaloalkoxy, aminothio, aminosulfinyl, aminosulfonyl, alkylsulfonylamino, alkenylsulfonylamino, alkynylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, hydroxy, acyl, carboxy, aminocarbonyl, alkylcarbonyl, alkoxycarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylcarbonyl, arylcarbonyloxy, arylcarbonylamino, heteroarylcarbonyl, heteroarylcarbonyloxy, heteroarylcarbonylamino, cyano, nitro, alkenylcarbonylamino, alkynylcarbonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, alkynylaminocarbonylamino, arylaminocarbonylamino, heteroarylaminocarbonylamino, alkoxycarbonylamino, alkenyloxycarbonylamino, alkynyloxycarbonylamino, aryloxycarbonylamino, heteroaryloxycarbonylamino, aminocarbonylamino, alkylaminocarbonyloxy, alkoxycarbonylamino, 1,1-(alkoxy or aryloxy)<sub>2</sub>alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring), S(O)<sub>2</sub>R<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkenyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)alkynyl, -NR<sup>6</sup>(C=NR<sup>7</sup>)heteroaryl, -NR<sup>8</sup>(C=NCN)-amino,



pyridine-N-oxide,



(where Q is O or H<sub>2</sub> and n' is 0, 1, 2 or 3) or

$\text{---C}(\text{NR}^8\text{R}^9)=\text{CH---C}(=\text{O})\text{---R}^{8a}$ ; tetrazolyl, pyrazolyl, pyridyl, thiazolyl, pyrimidinyl, imidazole, oxazole, or triazole, -PO(R<sup>13</sup>)(R<sup>14</sup>), (where R<sup>13</sup> and R<sup>14</sup> are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); and may be optionally independently substituted with from one to five substituents, which may be the same or different;

including pharmaceutically acceptable salts thereof, prodrugs thereof, and all stereoisomers thereof; with the proviso that where Z is imidazole-4-yl, 5-alkylimidazol-4-yl or 5-cyclohexylimidazol-4-yl, then R<sup>1</sup> cannot be benzoxazole, benzthiazole, benzimidazole or pyridine].--



--71. (Amended) The compound as defined in Claim 64 wherein R<sup>1</sup> is

